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Experimental Studies on Influences of Portal Vein Interruption on the Pancreas

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Introduction

At operation for malignant diseases of the liver, bile duct, and pancreas, the portal vein is sometimes resected with tumor of these organs in order to improve operative radicality. In these operations, transient portal vein interruption is necessary. PRINGLE's manuplation that cramps the hepatoduodenal ligament is used as the method to arrest hepatic bleeding²⁴⁾. There are many reports concerning influences of acute interruption of the portal vein on the general conditions^{2,11,23)}, liver¹⁴⁾, heart¹⁸⁾ and intestine²⁾, however the study concerning the pancreas in such a situation is very rare. The author observed the chemical and histological changes of the rat pancreatic tissue during and after continuous or divided portal vein interruption, and the effects of premedication with protease inhibitors on the pathological conditions were also investigated.

Materials and Methods

I. Experimental animals

Three hundred and seven Wistar male rats weighing from 250 to 300 g were used.

II. Experimental methods

After 24 hours fasting, rats were anesthetized with intraperitoneal pentobarbital (6 mg/100 g body weight). Through a midline abdominal incision, the portal vein was separated from the surrounding tissues and clamped using a vessel clip at the part of hepatic hilus. Changes during portal vein clamping and after recirculation of the portal system were studied as follows. Experiment 1: The relations of clamping time with changes of the general condition and the pancreas were studied. Rats were divided into the following 4 groups.

- | | |
|-------------------------------|--------|
| (1) Control group | (n=44) |
| (2) 10 minutes clamping group | (n=41) |
| (3) 20 minutes clamping group | (n=71) |
| (4) 30 minutes clamping group | (n=34) |

Key words: Portal vein, Pancreas, Protease inhibitor.

索引語: 門脈, 膵, 蛋白分解酵素阻害剤.

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Experiment 2: Continuous clamping was compared with divided one in the following 2 groups.

- (1) Continuous clamping for 20 minutes (n=71)
- (2) Divided clamping for 20 minutes with 10 minutes recirculation (n=78)

Experiment 3: Influences of premedication with a protease inhibitor, 6-amidino-2-naphthyl 4-guanidinobenzoate dimethanesulfonate (ANG), were studied in the following 2 groups.

- (1) Nontreated group (clamping time, 20 minutes) (n=71)
- (2) Treated group (ANG was given 10 mg/kg body weight into the peritoneal cavity 15 minutes before portal vein clamping, aiming that blood concentration of ANG became highest at the time of clamping (clamping time, 20 minutes) (n=39)

III. Items of observation

Changes following the portal vein interruption were observed in the two aspects. One was influences on the general condition and another was changes of the pancreas.

1. Influences on the general condition

- (1) Mortality rate: This was estimated at 3 hours after the release of portal vein clamping.
- (2) Femoral artery pressure: The femoral artery was cannulated with a polyethylene tube and the opposite end of the tube was connected to the pressure transducer (GOULD P23 ID, Statham), and the pressure was recorded on polygraphs (RM6000, Nihonkohden).
- (3) Serum amylase activity was measured by the blue starch method.
- (4) Serum acid phosphatase activity was measured by Kind King's method

2. Changes of the pancreas

- (1) Oxygen saturation in the tissue was measured with pan oximeter HSO-6 (Arrow)¹³⁾. That of the liver, stomach and caecum was also measured as control.
- (2) Wet weight was measured as total weight of the pancreas.
- (3) Acid phosphatase activity in the homogenate: The pancreatic tissue was excized and rinsed with ice cold physiologic saline solution, thereafter the tissue was homogenated with ice cold 0.25 M sucrose including Triton X-100, in a 1 : 9 ratio of the tissue : sucrose. Specific activities were measured by the method of ANDERSCH¹⁾ and were expressed as amounts of p-nitrophenol (μmol)/hour/mg protein. Protein was measured by the method of LOWRY et al¹⁶⁾.
- (4) Light microscopic study: The pancreatic tissue was excized immediately after vital fixation and was stained with hematoxylin-eosin and iron-hematoxylin.
- (5) Electron microscopic study: The pancreatic tissue was fixed with 2.5 per cent glutaraldehyde solution and postfixed with 1 per cent osmium tetroxide. The tissue was dehydrated in graded concentration of acetone and embedded in Epok 812. Thin sections cut with a Portar-Blum MT II B ultramicrotome were stained with uranyl acetate and leadacetate. Observations were carried out with Hitachi HU-II A type electron microscope.

Light and electron micrographs of the pancreas were observed immediately after the release of clamping, and 3, 6 and 24 hours later. Blood sugar level, serum amylase activity, serum

acid phosphatase activity, wet weight of the pancreatic tissue, and acid phosphatase activity in the homogenate of the pancreatic tissue were observed 3, 6 and 24 hours after the release of clamping. The femoral artery pressure and oxygen saturation in the tissues were observed during the clamping and soon after the release of clamping.

IV. Calculations

The data obtained were evaluated for statistical significance by means of Student's t-test or, in the case of mortality rate, χ^2 exact test.

Results

Experiment 1.

1. Influences on the general condition

(1) Mortality rate

The rates of the control, 10-min-clamping, 20-min-clamping and 30-min-clamping groups were 0% (0/38), 3.2% (1/31), 17.7% (11/62) and 41.4% (12/29), respectively. There was a significant difference between the 10-min-clamping and 20-min-clamping groups ($p<0.05$), and also between the 20-min-clamping and the 30-min-clamping groups ($p<0.05$). In the 30-min-clamping group, nearly half of rats died within 3 hours after the release of clamping. This group was excepted from the following experiment, because of its high mortality.

(2) The femoral artery pressure

The arterial pressure decreased immediately after the clamping, and finally fell down to

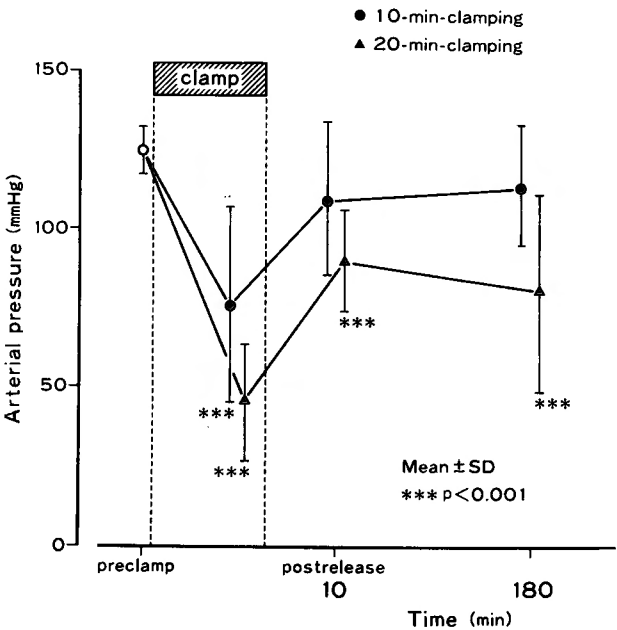


Fig. 1. Changes of maximum femoral artery pressure.

75 mmHg in the 10-min-clamping group and 50 mmHg in the 20-min-clamping group. After the release of clamping, the arterial pressure gradually increased. Its recovery was faster in the 10-min-clamping group than the 20-min-clamping group. But there was no significant difference between the two groups (Fig. 1).

(3) Serum amylase activity

There was no change in the control group. In the clamping groups, it gradually increased with time lapse. This change was more remarkable in the 20-min-clamping group than in the 10-min. But there was no significant difference between the two (Fig. 2).

(4) Serum acid phosphatase activity

There was no change in the control group. But in the clamping groups, it gradually increased with time lapse. This change was more remarkable in the 20-min-clamping group than in the 10-min. And there was a statistically significant difference between the two, 3 hours after the release ($p < 0.05$) (Fig. 3).

2. Changes of the pancreas

(1) Oxygen saturation in the tissue

Relative saturation of oxygen in the pancreatic tissue showed below 50% during the clamping. This decrease was lowest among all the organs measured. Its post-releasing recovery in the pancreatic tissue was slow compared with other organs. There was a significant

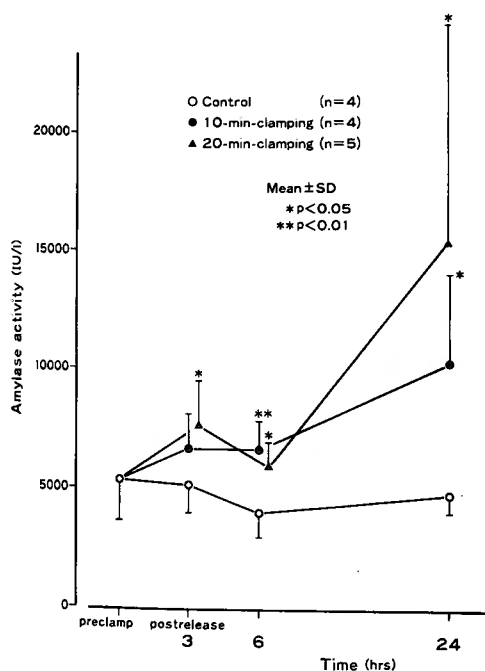


Fig. 2.

Fig. 2. Changes of serum amylase activity.

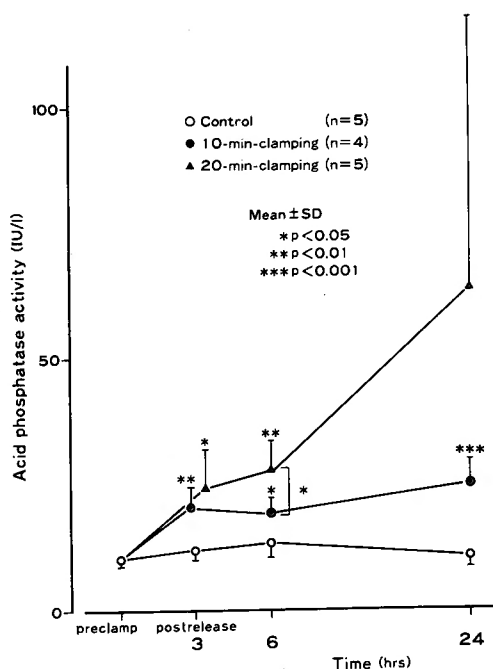


Fig. 3.

Fig. 3. Changes of serum acid phosphatase activity.

difference between the pancreas and other organs ($p < 0.01$). A change in the liver during and after the clamping was minimum among all the organs. A decrease of a saturation rate in the pancreatic tissue during clamping was not different between the 10-min and the 20-min clamping groups. But recovery of a saturation rate was significantly better in the former ($p < 0.001$) (Fig. 4).

(2) Wet weight

There was no remarkable change in the control group. In the clamping groups, it showed the maximum 3 hours after the release and gradually decreased. This change was more remarkable in the 20-min-clamping group than in the 10-min. There was a statistically significant difference between the two, 3 and 6 hours after the release ($p < 0.01$, $p < 0.01$) (Fig. 5).

(3) Acid phosphatase activity in the homogenate

In the control group, it slightly decreased after the release. In the clamping groups, it remarkably decreased and was lowest 3 hours after the release, and thereafter increased. This change was more remarkable in the 20-min-clamping group than in the 10-min. There was no significant difference between the two (Fig. 6).

(4) Light microscopic findings

In the 10-min-clamping group, congestion in the acinar tissue and islet, and tendency to increase zymogen granules in the acinar cell were observed immediately after the release. In the 20-min-clamping group, these changes were more remarkable, and in addition, some vacuolization in the acinar cell were also observed (Fig. 7).

(5) Electron microscopic findings

In the 10-min-clamping group, dilatation of the citerna in the rough endoplasmic

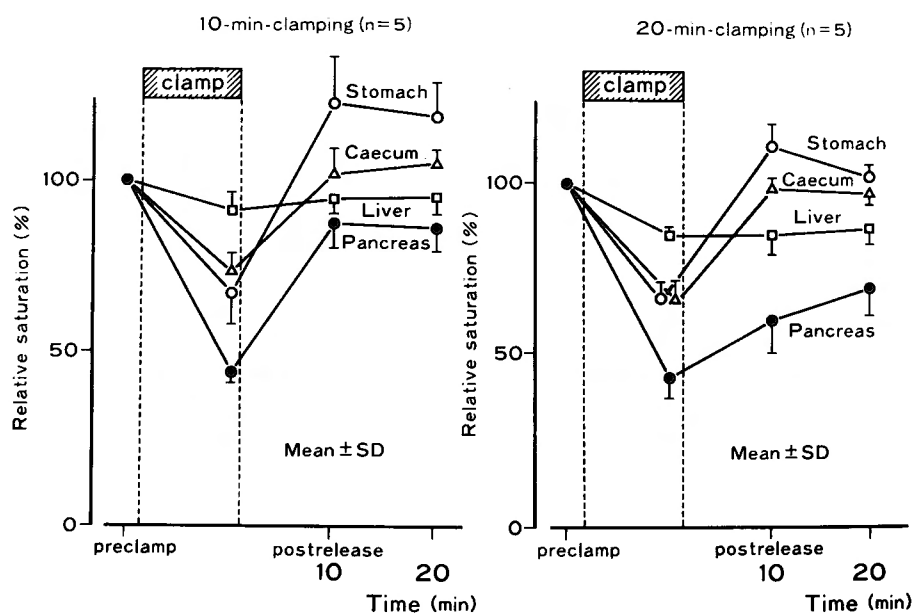


Fig. 4. Relative saturation of oxygen in the various organs.

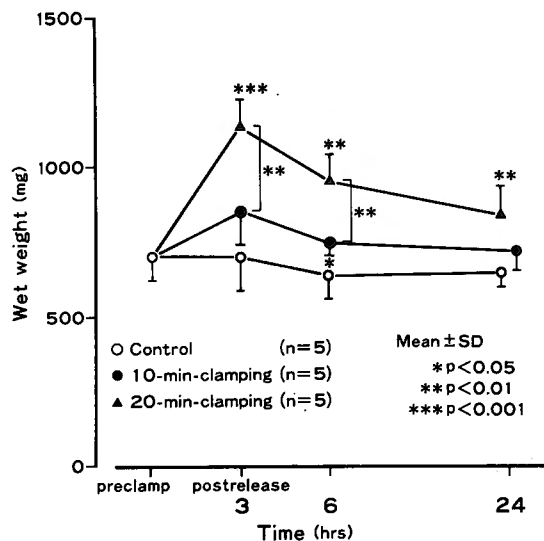


Fig. 5. Changes of wet weight of the pancreas.

reticulum, swelling of mitochondria and disarrangement of cristae were observed immediately after the release. In the 20-min-clamping group these changes were more remarkable and a large number of disruption of mitochondrial cristae were observed (Fig. 8). These light and electron microscopic changes maximumly appeared immediately after the release, and gradually relieved within 24 hours observation. But congestion was observed by light microscopy, and cytological changes in the rough endoplasmic reticulum and mitochondria, observed by

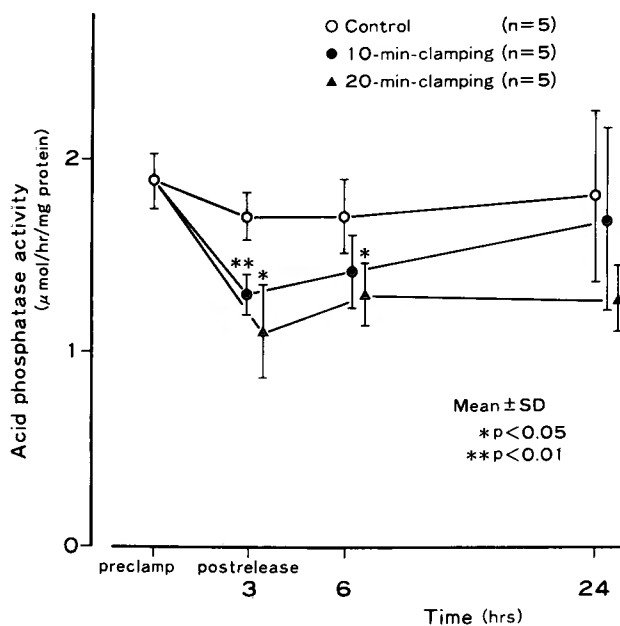


Fig. 6. Changes of acid phosphatase activity in the homogenate of the pancreas.

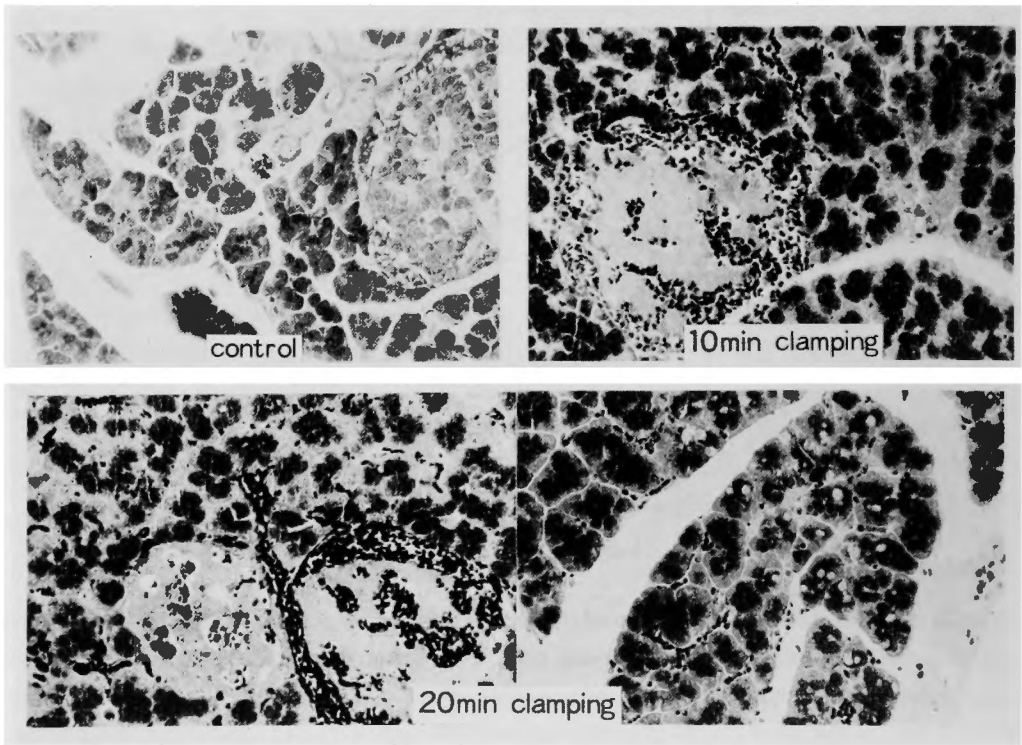


Fig. 7. Light micrographs of the pancreatic tissue immediately after the release of clamping. (Heidenhain's iron hematoxylin stain, $\times 200$)

electron microscopy, were retained untill 24 hours after the release.

Experiment 2

1. Influences to the general condition

(1) Mortality rate

In the continuous and divided clamping groups, the mortality rate was 17.7% (11/62) and 15.9% (11/69), respectively. There was no significant difference between the two.

(2) The femoral artery pressure and serum amylase activity

There was no significant difference between the two.

(3) Serum acid phosphatase activity

The activity was slightly lower in the divided-clamping group than in the continuous-clamping group 24 hours after the release. But there was no significant difference between the two.

2. Changes of the pancreas

(1) Oxygen saturation in the tissue

A decrease of saturation rates during the clamping was not different between the two. But its recovery after the release was significantly rapid in the divided-clamping group ($p < 0.01$)

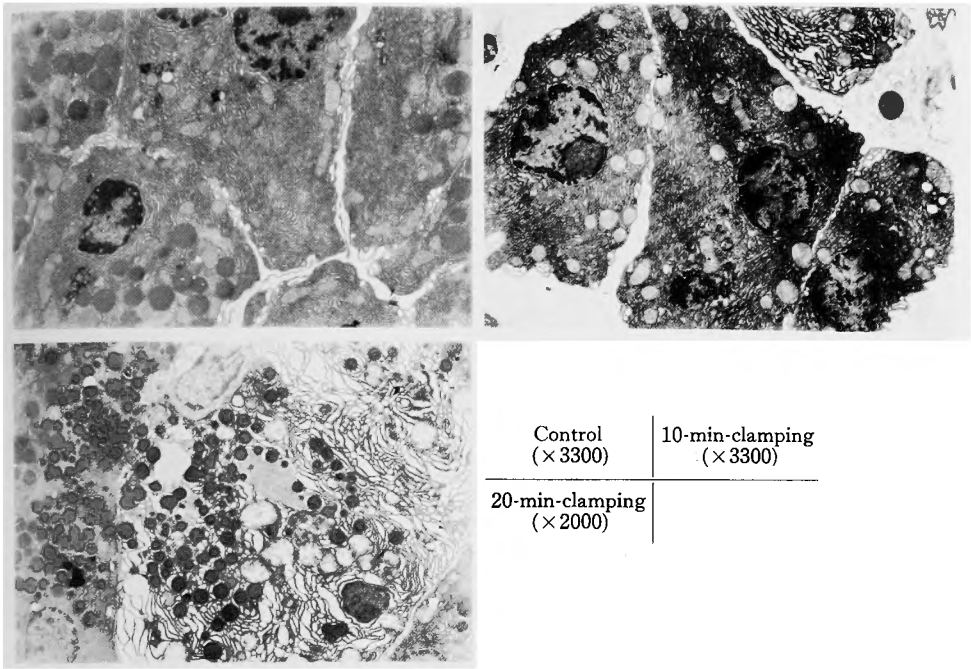


Fig. 8. Electron micrographs of the pancreatic cells immediately after the release of clamping.

(Fig. 9).

(2) Wet weight

Throughout the experimental course, the wet weight of the pancreas was slightly more in the divided-clamping group compared with the continuous-clamping group, however, there was no significant difference between the two (Fig. 10).

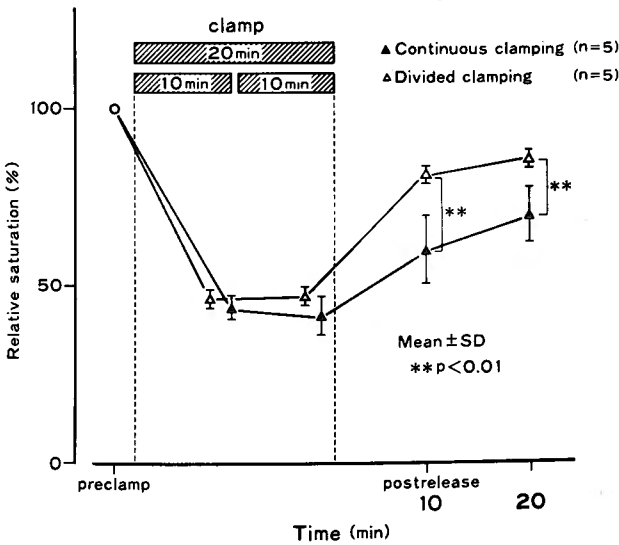


Fig. 9. Relative saturation of oxygen in the pancreatic tissue.

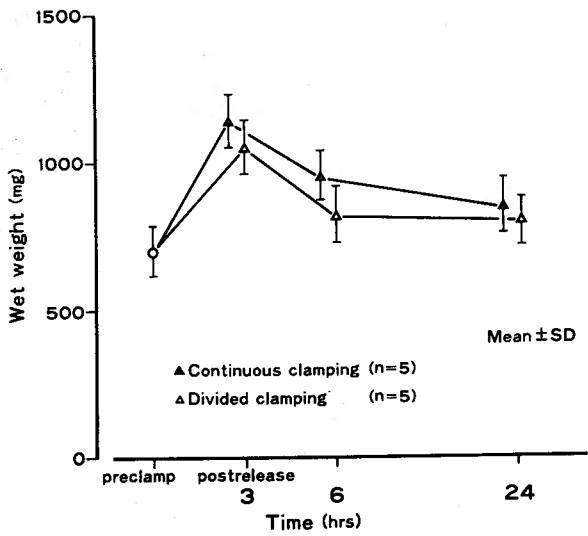


Fig. 10. Changes of wet weight of the pancreas.

- (3) Acid phosphatase activity in the homogenate
No difference was observed between the two.

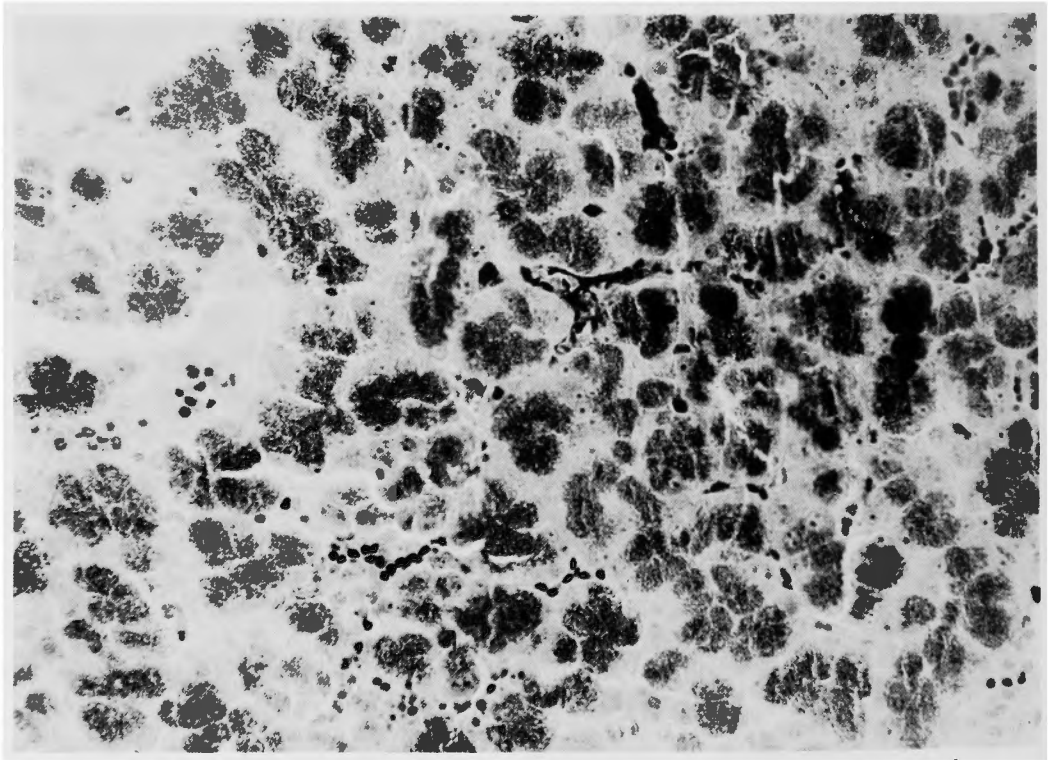


Fig. 11. Light micrograph of the pancreatic tissue in the divided clamping group immediately after the release of clamping. (Heidenhain's iron hematoxylin stain, $\times 200$)

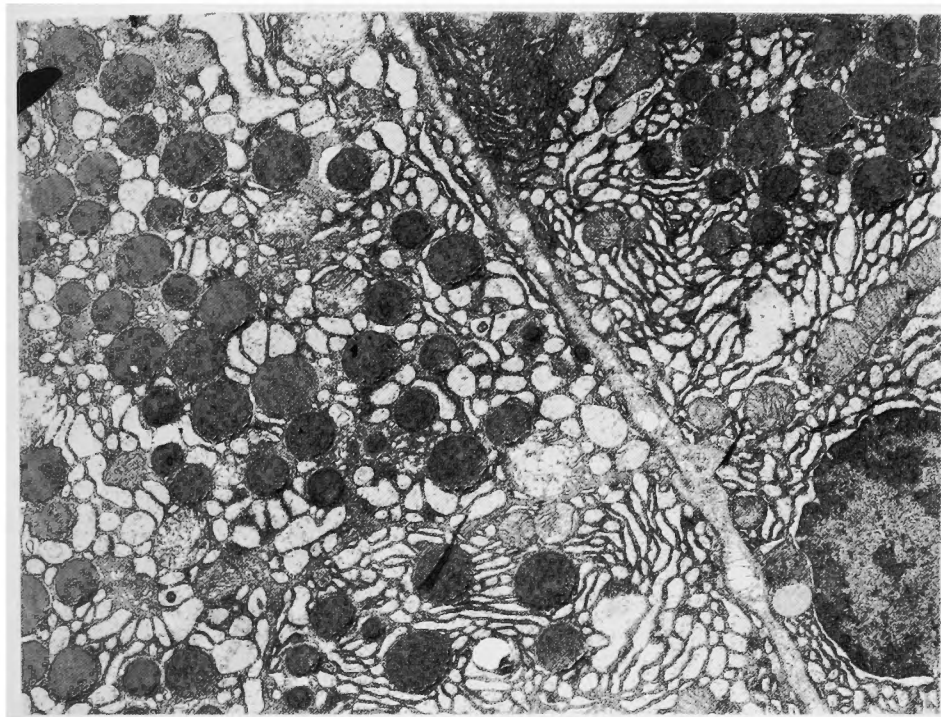


Fig. 12. Electron micrograph of the pancreatic cells in the divided clamping group immediately after the release of clamping. ($\times 3300$)

(4) Light microscopic findings

Histological changes in the two groups were considered to be almost the same. But in the divided-clamping group, no vacuolization in the acinar cell was observed (Fig. 11).

(5) Electron microscopic findings

Cytological changes in the divided-clamping group were similar to those in the continuous-clamping group (Fig. 12). There was no obvious difference between the two.

Experiment 3

1. Influences on the general condition

(1) Mortality rate

In the treated and nontreated groups, mortality rate was 0% (0/38) and 17.7% (11/62), respectively. There was a significant difference between the two ($p < 0.05$).

(2) The femoral artery pressure

In the treated group, the pressure fall during the clamping was less and its recovery after the release was better, compared with that in the nontreated group. But there was no significant difference between the two (Fig. 13).

(3) Serum amylase activity

Changes of amylase activity in the two groups were almost the same (Fig. 14).

(4) Serum acid phosphatase activity

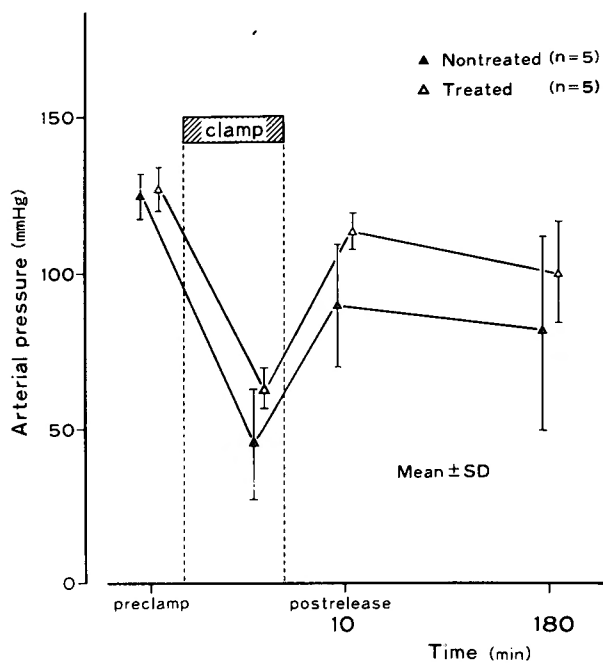


Fig. 13.

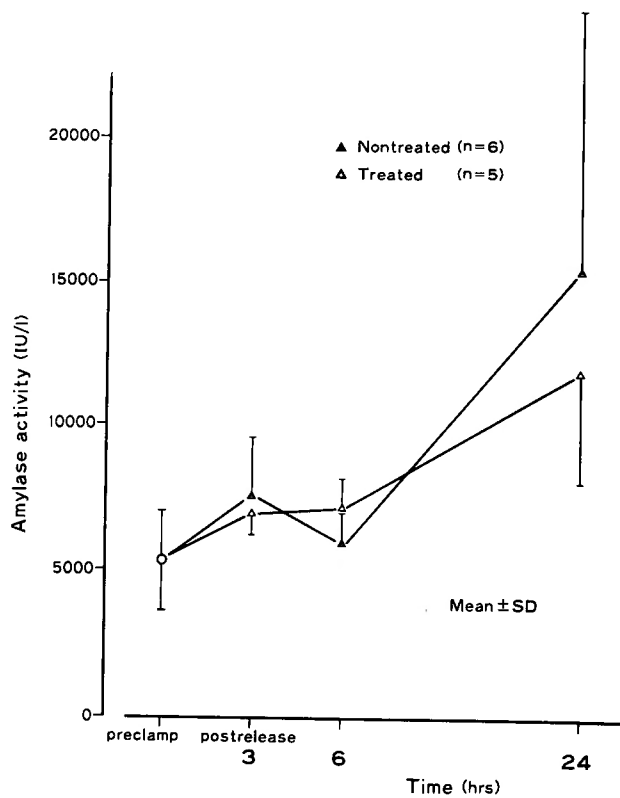


Fig. 14.

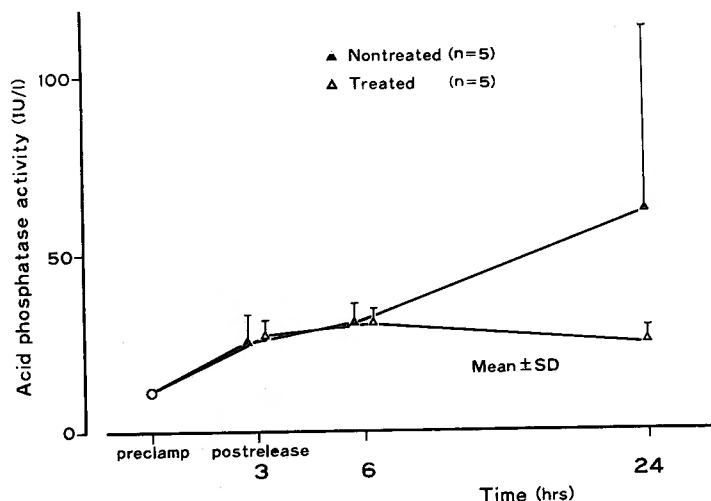


Fig. 15. Changes of serum acid phosphatase activity.

An elevation of the activity 24 hours after the release was slight in the treated group, compared with that in the nontreated group. But there was no significant difference between the two (Fig. 15).

2. Changes of the pancreas

(1) Oxygen saturation in the tissue

In the treated group, a decrease of the saturation during the clamping was significantly less ($p < 0.001$), and its recovery after the release was also significantly better ($P < 0.001$), than

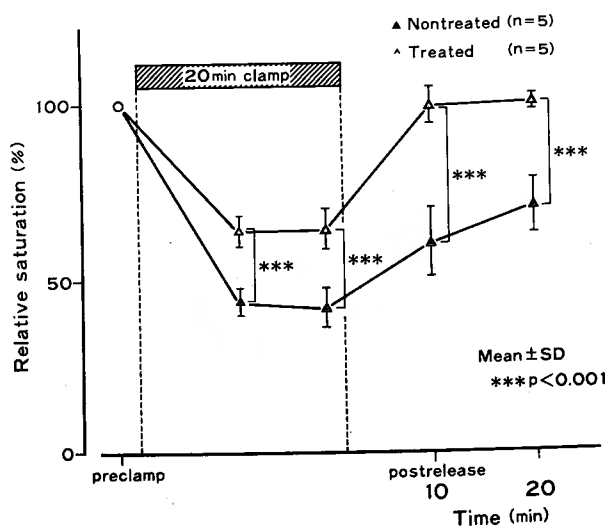


Fig. 16. Relative saturation of oxygen in the pancreatic tissue.

Fig. 13. Changes of maximum femoral artery pressure.

Fig. 14. Changes of serum amylase activity.

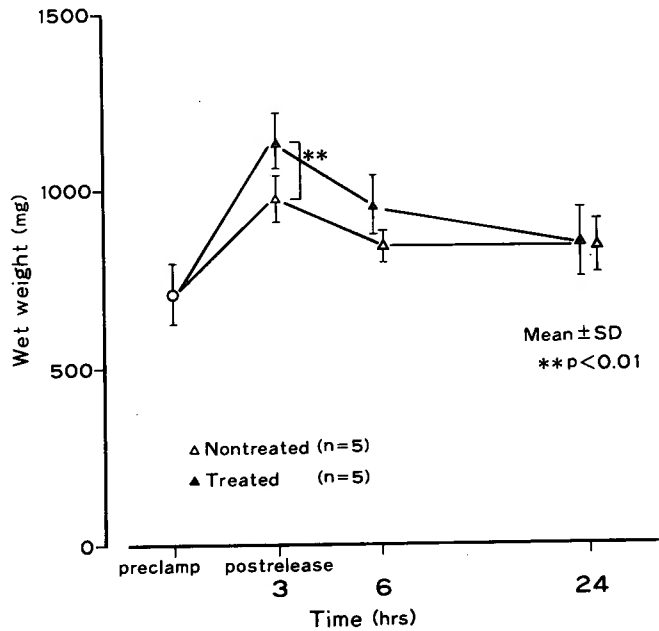


Fig. 17. Changes of wet weight of the pancreas.

that in the nontreated group (Fig. 16).

(2) Wet weight

Throughout the experimental course, the weight change was less in the treated group than in the nontreated group. The difference was most significant 3 hours after the release ($p < 0.01$) (Fig. 17).

(3) Acid phosphatase activity in the homogenate

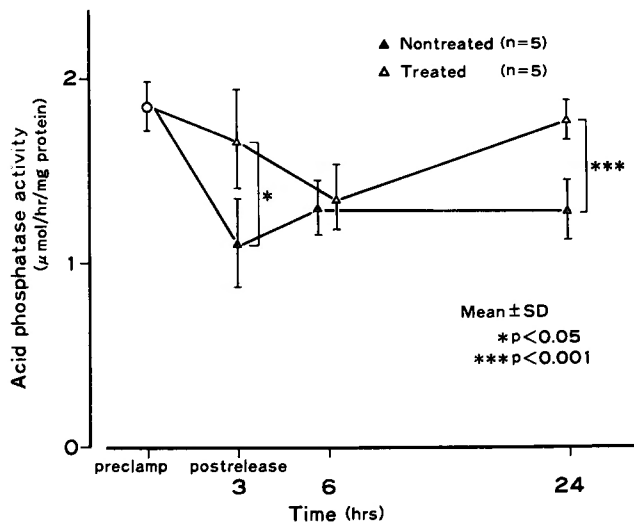


Fig. 18. Changes of acid phosphatase activity in the homogenate of the pancreas.

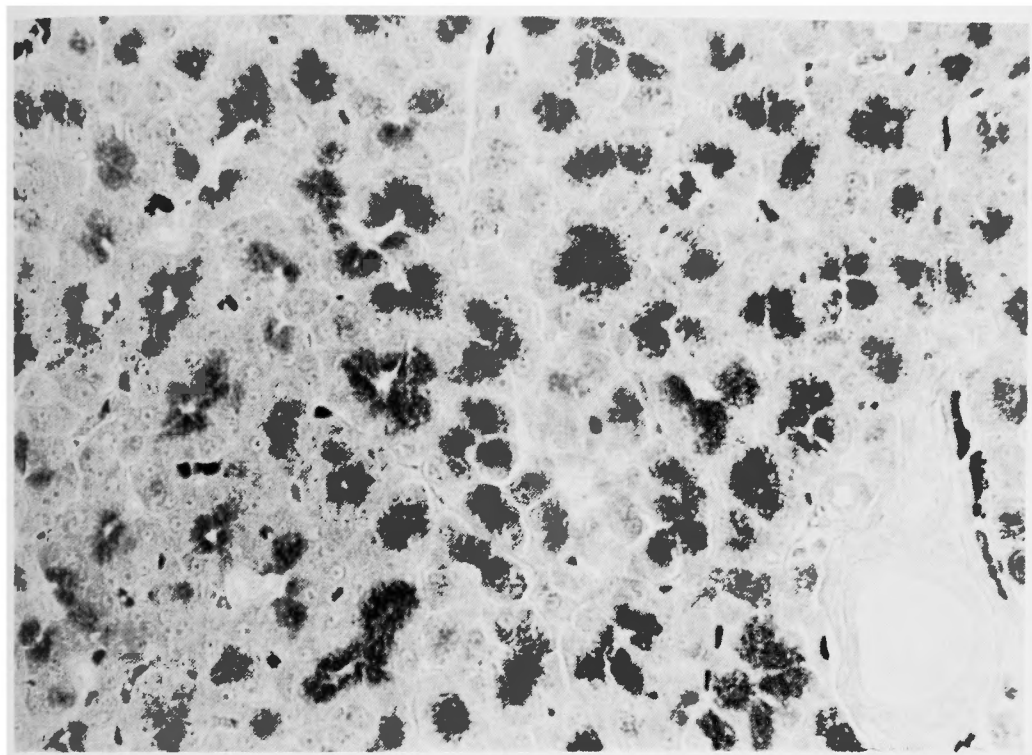


Fig. 19. Light micrograph of the pancreatic tissue in the treated group immediately after the release of clamping. (Heidenhain's iron hematoxylin stain $\times 200$)

A decrease of the activity was delayed in the treated group and the activity was lowest 6 hours after the release. Its recovery 24 hours after the release was significantly better than that in the nontreated group ($p < 0.001$) (Fig. 18).

(4) Light microscopic findings

Histological changes in the treated group was considered to be more slight compared with that in the nontreated group, i.e., an increase of zymogen granule in the acinar cell was slight and vacuolization in the acinar cell was not observed in the treated group (Fig. 19).

(5) Electron microscopic findings

Cytological changes in the treated group was considered to be more slight compared with that in the nontreated group, i.e., dilatation of cisternae in the rough endoplasmic reticulum was slight and no structural change of mitochondria was observed in the treated group (Fig. 20).

Discussion

It is well known that acute and complete portal vein interruption in animals is fatal²³. This kind of death is caused, in many cases, by 1) hypovolemic shock following blood pooling in the splanchnic area¹¹, 2) disseminated intravascular coagulopathy (DIC) accompanied with endotoxemia^{20, 22}, 3) hemorrhage from the intestine¹⁷, 4) hyperpotassemia⁵ and 5) disturbance

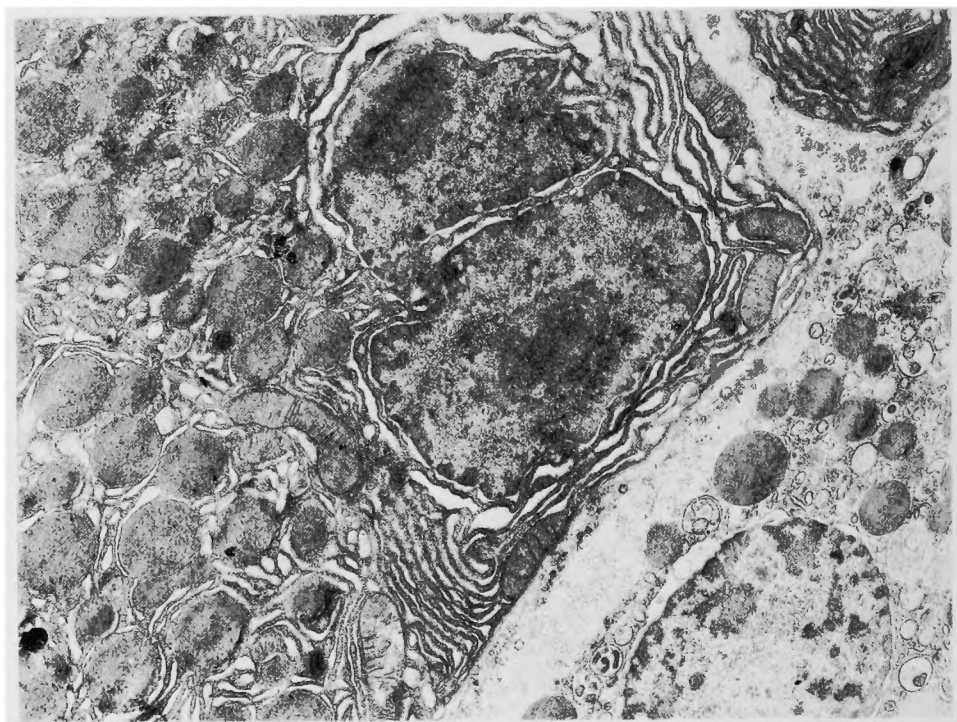


Fig. 20. Electron micrograph of the pancreatic cells in the treated group immediately after the release of clamping. ($\times 3300$)

of acid-base balance⁴⁾. If portal vein interruption is carried out for a short time, these changes are reversible²⁵⁾. This permissible interruption time is different in species⁷⁾. Man and monkey can tolerate portal vein interruption longer than other animals, because of the well developed collateral circulation of the portal vein. But even in man, there are variations in the development of collaterals. In operations for malignant diseases, there are some possibilities that the collateral circulation decreases owing to an extended lymph node dissection.

There have been published many reports concerning injuries of the organs, especially the liver¹⁴⁾, heart¹⁸⁾ and intestine²⁾, from several aspects. However there is no noticeable report concerning injuries of the pancreas, except the report by BRODETTI⁶⁾.

On the other hand, the pancreas is sometimes influenced by experimental shock or ischemia³⁰⁾ and in addition, easily disturbed by experimental endotoxemia¹⁰⁾. The pathophysiology following portal vein interruption is very complex. One of the main pathological conditions is hypovolemic shock caused by peripheral blood pooling in the splanchnic area, imposing congestion on the pancreas. And another is endotoxemia. Therefore the author undertook this experiment to examine some changes of the pancreas during and after portal vein interruption.

First of all, the mortality rate was investigated to realize the permissible limit of an interruption time in rats. The longer the portal vein interruption, the more the mortality rate. In the 30-min-clamping group, rats died more than 40% within 3 hours, and nearly 70% within

24 hours after the release, respectively. From these results, the 30-min-clamping group was considered as inadequate because of its high mortality, and then excluded from the following experiment.

The femoral artery pressure fell immediately after the interruption, because the circulating blood volume decreased due to the peripheral blood pooling in the splanchnic area. After the release of interruption, the pressure was elevated but did not recover to the pre-interruption level, and gradually decreased. These phenomena implied that rats were still under a shock state.

Serum amylase activity gradually increased for the first 24 hours after the release and returned to the normal 48 hours after. Serum amylase activity is also originated in the salivary gland³⁾ and its level is influenced by the renal function¹⁹⁾. But the author considers that based upon the histological changes of the pancreas, the injury of the pancreas was one of the causes of the increase of serum amylase activity in this experiment.

The serum acid phosphatase activity showed similar changes to that of amylase. Acid phosphatase is well known as one of the lysosomal enzymes. In general, lysosomal enzyme was reported to increase in the peripheral blood during some kinds of shock and to play an important role in progress of shock⁹⁾. Portal vein interruption may become one of the causes of severe shock, and lysosomal membranes may be disrupted by tissue hypoxia resulting from shock, and then acid phosphatase activity may increase in the peripheral blood.

Oxygen saturation in the various abdominal organs remarkably decreased during the interruption. The decrease and its recovery after the release was not so good in the pancreas compared with the liver, stomach and caecum. OGAWA et al.²¹⁾ reported that pancreatic blood flow tended to decrease during shock, and then it gave rise to ischemia in the pancreatic tissue. JONES et al.¹²⁾ also reported that the pancreas was one of the organs easily influenced by ischemia. Judging from the results of oxygen saturation, the author considers that hypoxia of the pancreatic tissue may be one of the causes of these changes in this experiment. Despite the same level of decrease of saturation ratio during the interruption in the 10-min-clamping and 20-min-clamping groups, the recovery after the release was significantly slower in the latter. It was considered as its reason that thrombosis was formed in the vessels and hypoxia continued even after the release of interruption in the 20-min-clamping group. As the reason why change of the liver was minimum, it was considered that blood flow from the hepatic artery was maintained.

Wet weight of the pancreas was supposed to increase in the clamping groups because of congestion or edema secondary to it. Acid phosphatase activity in the homogenate of the pancreas decreased in the clamping group. LEFER et al.¹⁵⁾ and OGAWA et al.²¹⁾ supposed that an increase of its activity in the peripheral blood during shock was derived from the pancreas. LEFER¹⁵⁾ also presumed that a decrease of the activity in the pancreatic tissue was resulted from its release into the peripheral blood. OGAWA²¹⁾ reported that elevation of its activity in serum was suppressed in previously pancreatectomized rabbits. There is a possibility in this experiment that acid phosphatase originated in the pancreas was released into the peripheral circulation, because of hypoxia in the pancreatic tissue caused by portal vein interruption. But the liver,

spleen and kidney contain a larger quantity of lysosomal acid phosphatase than the pancreas, and these organs might release the enzyme during portal vein interruption. Therefore it can not be concluded that the pancreas is an only origin of elevated activity of acid phosphatase in the peripheral blood.

Light microscopy showed congestion, which was more remarkable in the islet than in the acinar tissue, as a main pathological change. This is considered to be contributed to the fact the capillaries are more developed in the islet than in the acinar tissue. Vacuolization in the acinar cell was observed in the 20-min-clamping group. The entity of this vacuolization is obscure. Vacuolization in the acinar cell is said to be observed under the circumstances of experimental obstructive jaundice²⁶⁾ or experimental acute pancreatitis²⁸⁾. It is difficult to explain the mechanism of the vacuolization in detail, but it is supposed to be related to damage or degeneration of the acinar cell. Zymogen granules increased in number in the clamping groups. This mechanism is obscure too, but the author supposes that this phenomenon depends upon acceleration of production or inhibition of excretion of zymogen granules during portal vein interruption.

Pathological changes in electron microscopy were mainly observed in the rough endoplasmic reticulum and mitochondria. These findings, which were similar to those resulting from ligation of the pancreatic duct²⁷⁾, administration of endotoxin¹⁰⁾ or ischemia in vivo¹²⁾, were observed as a focal change of the pancreas.

Histological changes were considered to be reversible, because no necrotic cell was observed and the changes became slight with the lapse of releasing time.

All changes of experiment 1 were more remarkable in the 20-min-clamping group than in the 10-min. Changes of the whole body and pancreas during and after portal vein interruption were in proportion to the length of interruption time. As a result of experiment 1, it was confirmed that several pathological and biochemical changes occurred in the pancreas as well as other organs which had been previously reported.

In order to reduce the above described changes, divided portal vein interruption and premedication with a protease inhibitor were attempted by the author. Divided portal vein interruption sometimes carried out in practice of abdominal surgery when interruption needs a long time. As a result of experiment 2, there was no difference between the divided-clamping group and the continuous-clamping group concerning influences to the general condition, however, recovery of oxygen saturation in the pancreatic tissue after the release was better, and changes of wet weight and light microscopic findings were more slight in the divided-clamping group. The effect of divided interruption in this experiment was not so much obtained as expected.

Some protease inhibitors are clinically used for treatment of acute pancreatitis⁸⁾ or DIC²⁹⁾. The author used this drug in expectation of two effects; a direct effect to the pancreas, and a systemic effect against DIC. By this treatment, in fact, general conditions, such as mortality rate, femoral artery pressure and serum acid phosphatase, and all changes in the pancreas were improved. Such improvement might be caused not only by the effect on the pancreas, but also by systemic effect against DIC. Degradation time of this protease inhibitor in blood is very short, and

therefore one shot administration into the peritoneal cavity, as done in this experiment, is supposed to be not so effective. If continuous intravenous administration of this drug was attempted, a more remarkable effect might be expected. Thus, it is necessary to consider several influences of portal vein interruption on the pancreas, when the interruption time exceeds a safe limit. The protease inhibitors may be effective for reduction of these pathological phenomena.

Summary

1. As regards influences of portal vein interruption on the general condition, an increase of serum amylase activity and acid phosphatase activity, a decrease of the femoral artery pressure, were observed.
2. Under these circumstances, a decrease of saturation of tissue oxygen and acid phosphatase activity, an increase of wet weight, and histological changes by light and electron microscopy were observed in the pancreas.
3. These changes were more remarkable in the 20-min clamping group than the 10-min.
4. These changes were not reduced by divided portal vein interruption.
5. These changes were slightly reduced by premedication with a protease inhibitor (ANG).
6. Thus, it is necessary to consider several influences of portal vein interruption on the pancreas, too, when the interruption time exceeds a safe limit.

Acknowledgement

The author is indebted to Prof. Masaharu Katsumi, Dr. Yozo Aoki and colleagues, Department of Gastroenterological Surgery, Wakayama Medical College, for their continuing guidance and encouragement, and to Prof. Kimie Fujie and Dr. Junichi Hiraoka, the Second Department of Anatomy, Wakayama Medical College, for their technical guidance throughout the experiment.

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和文抄録

門脈一時遮断の脾に及ぼす影響に関する実験的研究

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門脈一時遮断時および遮断解除後の脾の変化をラットを用い観察し以下の結論を得た。全身的には血清 amylase 活性，血清 acid phosphatase 活性の上昇，大腿動脈圧の低下が観察された。脾においては組織酸素飽和度，ホモジェネート中 acid phosphatase 活性の

低下，湿重量の増加，光顕像および電顕像での種々の変化が観察された。上記の変化は遮断時間が長いほど著しい傾向にあった。上記の変化は分割門脈遮断によってはあまり軽減されなかったが，蛋白分解酵素阻害剤の前投与によりやや軽減された。